Anti-Osteoporosis effects of Alderonate or Parathyroid Hormone on the union of Osteoporotic Distal Radius Fractures

Abstract

Background: Osteoporosis is the most common bone metabolic disease. The purpose of this study was to evaluate the effect of anti-osteoporosis treatment with bisphosphonate and parathyroid on bone repair in patients with osteoporosis related fractures.

Methods: This single-blind randomized controlled clinical trial was performed on three groups of 20 patients each (parathyroid hormone, alendronate and control) with osteoporosis fractures hospitalized in orthopedic ward of Emam Khomeini and Boali Sinaye Sari hospitals during 2016-2018. All the patients were assessed at the 4th, 8th, and 12th week in terms of union.

Results: While no union was reported at the end of the fourth week, 20, 18, and 17 subjects respectively on CinnoPar, alendronate and control groups had union at the end of the eighth week. Furthermore, the complete union was achieved for all patients in the 12th week.

Conclusions: According to the results of the study, no significant difference was observed in the repair of osteoporotic fractures of distal radius by alendronate and parathyroid hormone.

Keywords: Osteoporosis, Alendronate, Parathyroid, Radius Distal

Introduction

Osteoporosis is the most common metabolic bone disease that decreases bone mass and destroys the microscopic structure of the specific bone, ultimately leading to bone fragility and increased risk of fracture\(^1\). In addition, osteoporosis is an asymptomatic condition and is caused due to fractures at old ages, thereby making it an important public health issue\(^2\). The prevalence of osteoporosis in women over 50 years of age in Iran was 6%, and the incidence of pelvic fracture in Iran was in 2003 was 20.6 women and 17.5 men per 100000 individuals\(^3\). In addition, approximately 10 million American women have osteoporosis\(^4\), and more than 300000 pelvic fractures occur in the United States due to osteoporosis every year. The cost of care for these patients reached $18 billion in 2005. Given the population ageing, it is predicted that this cost will reach $25.3 billion by 2025\(^5\).

According to the guidelines of the International Osteoporosis Foundation, 19% of male elderlies and 30% of female elderlies in the United States are at risk of fracture and require drug therapy\(^6\). Osteoporosis treatment is carried out to prevent the fracture of peripheral bones and vertebrae, for which various drugs can be used. The first step in the treatment of osteoporosis is using bisphosphonates (e.g., alendronate and risedronate) that act by inhibiting the activity of osteoclasts and reducing bone resorption\(^6\). While bisphosphonates do not create new bones, they can
increase bone mineral density (BMD) by 3% in a year and decrease the risk of bone fractures up to 40%. Nevertheless, 60% of the risk of fractures remains in the treatment of bisphosphonates, which leads to an increase in death rates due to osteoporosis fracture, even in the treated population\(^7\). There are other antiresorptive drugs in addition to bisphosphonates, including raloxifene, denosumab, and odanacatib.

Raloxifene only reduces the risk of spinal cord fracture by up to 50%\(^1\), whereas denosumab increases BMD by 4% in a year and does not decrease the risk of fracture\(^9\). Odanacatib is also a new antiresorptive drug that increases BMD level by 3.5% in a year\(^10\). It is notable that all of the mentioned drugs decrease bone resorption\(^1\) while maintaining the microscopic structure of trabecular bone\(^11\). However, these drugs increase bone density by filling ossification units and secondary mineralization and not by increasing the trabecular bone width\(^12\), which suggests the limited ability of the mentioned drugs to increase BMD. Therefore, a drug is required to stimulate ossification, cause the formation of a new high-quality bone, and reduce the risk of fracture\(^13,14\).

Human parathyroid hormone (hPTH (1-34)) or teriparatide is a bone anabolic agent. While the continuous and excessive PTH production in patients with hyperparathyroidism has catabolic effects on the bone, the alternate subcutaneous injection of PTH leads to anabolic effects on the bone, reported in 1930\(^15\). The subcutaneous injection of PTH increases PTH levels up to 10 times the normal range in 15-45 minutes. After 10-12 hours, the PTH levels return to the base level\(^16\). Pulse therapy with PTH provides a very distinct pattern of anabolic effects in the bone, determined with the increase of number, maturity, and activity of new osteoblasts and decrease of osteoblast apoptosis\(^15\). In addition, the production of bone matrix increases and leads to an increase in the volume of trabecular bone and its width, despite incomplete secondary mineralization of matrix\(^17,18\).

Moreover, teriparatide affects the cortical bone and increases its thickness. Increased bone formation and decreased bone absorption in endosteal and periosteal cortex areas increase bone diameter\(^17,19,20\). Furthermore, PTH considerably affects BMD. In the biggest study of PTH therapy in postmenopausal women, BMD of lumbar spine increased by 9% and 13% after 18 months of treatment for 20 μg and 40 μg subcutaneous injection of PTH, respectively\(^21\). In 1637 women with severe osteoporosis after menopause, new fractures for vertebra occurred 19 months after treatment in 15% of cases in the placebo group, but only 5% and 4% in the group treated with 20 μg and 40 μg PTH, respectively. These numbers are interpreted as decreased risk of fracture by 65% with 95% confidence interval in treatment with 20 μg PTH and by 69% with 95% confidence interval in treatment with 40 μg PTH. Moreover, patients under treatment less experience peripheral fractures, which was 3% and 6% in the PTH and placebo groups, respectively. In addition, the risk of fracture decreased by 53% and 54% in treatment with 20 and 40 μg PTH, respectively\(^22\).

The maximum duration of PTH treatment is two years, after which the benefits of the treatment are reduced. Therefore, the FDA suggests that patients receive PTH treatment for no more than two years. While the anabolic effects of PTH are not stable after discontinuation of treatment, the onset of the bisphosphonate at that time would result in maintaining BMD from the PTH treatment\(^12\). Although hPTH (1-34) has more effects over a shorter period, compared to bisphosphonates, it is still part of the second line of treatment due to concerns about possible complications, daily injections, and high costs. Given the lack of extensive studies on the effect of h PTH(1-34) in Iran, this study aimed to evaluate the effect of bisphosphonate anti-osteoporosis treatment and parathyroid on bone repair and
Methods

This single-blind randomized controlled trial was performed on patients with osteoporotic fractures hospitalized in the orthopaedic ward of Imam Khomeini and Boali Sina hospitals during 2016-2018. The research was approved by the ethics committee with the ethical code of IR.MAZUMS.REC.95.2767 and clinical trial code of IRCT20160830029603N6. The research population included all patients with osteoporotic fractures hospitalized in orthopaedic ward of Imam Khomeini and Boali Sina hospitals and underwent corrective surgery. Given the selection of all groups with the use of number table, the subjects were randomly allocated to research groups. To carry out blind research, radiographies of patients were provided to statistics specialists, who were unaware of the research groups and the treatment method, to record the union and non-union of each radiography.

Considering the sample size of previous studies and a 20% attrition, the sample size was estimated at 20 subjects per group. Inclusion criteria were age above 50 years, sudden fracture of the wrist, vertebra, or hip with a t-score below 2.5 treated with corrective surgery, and the lack of consumption of anti-osteoporosis drugs (e.g., bisphosphonate, calcitonin, raloxifene, and parathyroid hormone) during six months before the fracture. Exclusion criteria were a previous history of osteoporosis fracture, multiple traumas, cancer, diseases that require invasive, corticosteroid, or immunosuppressive treatments, and selected arthroplasty (Figure 1). At first, the research objectives were explained to the participants, and a written consent was obtained. Demographic characteristics of the subjects, including age, gender, weight, and body mass index (BMI) were recorded in the information form.

Moreover, the type (stable and non-stable) and place of fracture, type of surgery, and prosthesis used for each individual were recorded. After corrective surgery, patients were randomly divided into two groups of receiving anti-osteoporosis treatment using a random number table. After surgery and before discharge, the subjects of the first group received calcium osteoporosis treatment (1200 mg/day), vitamin D (800 IU/day), and alendronate (70 mg per week) for three months. On the other hand, the second group received calcium and vitamin D and parathyroid hormone injection (CinnoPar, manufactured by CinnaGen Co.) (0.08 cc/day) in the abdominal region (under the umbilical cord) or thigh for three months. The third group of included patients hospitalized in other parts of the orthopedic ward, who did not receive anti-osteoporosis treatment and were selected based on inclusion and exclusion criteria.

In public centers, the BMD test was carried out for all patients aged above 50 years with wrist fracture at the beginning of the study. One month after discharge, patients were followed up through a phone call in terms of taking medication and the capacity of accepting the treatment. In addition, patients were visited at the fourth, eighth, and 12th weeks and after the surgery to assess the level of union and radiography was requested for them. Eventually, data analysis was performed in SPSS version 16 using Chi-square. Furthermore, a P-value of below 0.05 was considered statistically significant.

Results

Table 1 shows the demographic features of subjects in three groups of the study based on gender. Of 20 subjects receiving CinnoPar and alendronate, four of the participants were male and the rest were female. In addition, three of the subjects in the control group were male and 17 were female (N=20).
Table 1. Frequency distribution of gender in patients of three groups hospitalized in two hospitals

<table>
<thead>
<tr>
<th>Gender</th>
<th>Frequency</th>
<th>Frequency percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>CinnoPar</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Alendronate</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Control</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>49</td>
</tr>
</tbody>
</table>

Table 2 shows the demographic characteristics of the subjects based on the mean age in three groups. The mean age of the patients in the CinnoPar group was 68.63, whereas it was 64.85 and 65.54 in alendronate and control groups, respectively.

Table 2. Frequency distribution of age in patients of three groups in two hospitals

<table>
<thead>
<tr>
<th>Age</th>
<th>Frequency</th>
<th>Mean</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>CinnoPar</td>
<td>20</td>
<td>68.63</td>
<td>54</td>
<td>90</td>
</tr>
<tr>
<td>Alendronate</td>
<td>20</td>
<td>64.85</td>
<td>54</td>
<td>83</td>
</tr>
<tr>
<td>Control</td>
<td>20</td>
<td>65.54</td>
<td>52</td>
<td>85</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>66.25</td>
<td>52</td>
<td>90</td>
</tr>
</tbody>
</table>

Table 3 shows the demographic characteristics of subjects based on frequency and percentage frequency of BMI of the participants. In this regard, the subjects receiving Cinno Par had a BMI of 27.24 while the participants in the alendronate and control groups had a BMI of 26.79 and 23.20, respectively.

Table 3. Frequency distribution of BMI in patients of three groups in two hospitals

<table>
<thead>
<tr>
<th>BMI</th>
<th>Frequency</th>
<th>Mean</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>CinnoPar</td>
<td>20</td>
<td>27.24</td>
<td>19.70</td>
<td>46</td>
</tr>
<tr>
<td>Alendronate</td>
<td>20</td>
<td>26.79</td>
<td>21.80</td>
<td>32.40</td>
</tr>
<tr>
<td>control</td>
<td>20</td>
<td>23.20</td>
<td>19.40</td>
<td>27.70</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>25.65</td>
<td>19.40</td>
<td>46</td>
</tr>
</tbody>
</table>

In Table 4, the union results of three groups in the fourth week are presented. As observed, none of the patients in the three groups of CinnoPar (patients receiving parathyroid hormone), alendronate (patients receiving alendronate) and control were eligible for fracture union in the fourth week.

Table 4. Chi-square results of reunion after the fourth week

<table>
<thead>
<tr>
<th>Variable</th>
<th>Classes</th>
<th>CinnoPar</th>
<th>Alendronate</th>
<th>Control</th>
<th>Chi-square Sig.</th>
</tr>
</thead>
<tbody>
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<td>-</td>
<td>-</td>
<td>-</td>
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<td></td>
<td>No</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

Table 5 contains the result of the comparison of union results in three groups in the eighth week. In addition, 20, 18, and 17 subjects in the CinnoPar, alendronate, and control groups had union, respectively. According to these results, the best union result was obtained in
the group receiving parathyroid hormone in the eighth week.

<table>
<thead>
<tr>
<th>Variable Class</th>
<th>Group</th>
<th>Chi-square</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Union</td>
<td>Yes</td>
<td>CinnoPar</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alendronate</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>CinnoPar</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alendronate</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>7</td>
</tr>
</tbody>
</table>

The idea of this research was obtained from clinical trials that have assessed the effectiveness of anti-osteoporosis drugs on hip fractures. According to the results of the present study, the anti-osteoporosis drugs of CinnoPar and alendronate were not effective in distal radius fractures, contrary to hip fractures. In other words, these drugs led to union with a delay. In this regard, while our findings are in line with the results of some studies, they are not in congruence with some other studies. For instance, Kim TY et al. (2012) evaluated the effect of different times of prescription of bisphosphonates on acceleration of intertrochanteric fracture and concluded that while the prescription of bisphosphonates in one week after fracture led to union on the 10th week, this process had no significant relationship with acceleration of union after the prescription of bisphosphonates on the first and third months. In the end, it was shown that bisphosphonate was unable to accelerate union in patients with intertrochanteric fractures. In other words, these drugs led to union with a delay. In this regard, while our findings are in line with the results of some studies, they are not in congruence with some other studies. For instance, Kim TY et al. (2012) evaluated the effect of different times of prescription of bisphosphonates on acceleration of intertrochanteric fracture and concluded that while the prescription of bisphosphonates in one week after fracture led to union on the 10th week, this process had no significant relationship with acceleration of union after the prescription of bisphosphonates on the first and third months. In the end, it was shown that bisphosphonate was unable to accelerate union in patients with intertrochanteric fractures. In this regard, our findings are in line with the aforementioned study since while all patients had a complete union at the end of the 12th week, all subjects in the parathyroid group reported complete union at the end of the eighth week. Nevertheless, there was no significant difference between the groups in terms of the pace of union.

In 2010, Aspenberg et al. performed a study on the role of teriparatide in radius distal fracture in postmenopausal women. According to previous animal research, it was aimed to determine whether the increased dose of teriparatide could decrease the time of union or not. Therefore, three groups, including control, alendronate (20 mg) and alendronate (40 mg), were assessed, concluding that even though teriparatide decreased the time of union, its increase did not accelerate the union process. In this regard, our findings are in line with the aforementioned study since while all patients had a complete union at the end of the 12th week, all subjects in the parathyroid group reported complete union at the end of the eighth week. Nevertheless, there was no significant difference between the groups in terms of the pace of union.

Moreover, Aspenberg and Johansson (2010) marked that teriparatide had an impact on early callus caused by radius distal fracture.

**Discussion**

The idea of this research was obtained from clinical trials that have assessed the effectiveness of anti-osteoporosis drugs on hip fractures. According to the results of the present study, the anti-osteoporosis drugs of CinnoPar and alendronate were not effective in distal radius fractures, contrary to hip fractures. In other words, these drugs led to union with a delay. In this regard, while our findings are in line with the results of some studies, they are not in congruence with some other studies. For instance, Kim TY et al. (2012) evaluated the effect of different times of prescription of bisphosphonates on acceleration of intertrochanteric fracture and concluded that while the prescription of bisphosphonates in one week after fracture led to union on the 10th week, this process had no significant relationship with acceleration of union after the prescription of bisphosphonates on the first and third months. In the end, it was shown that bisphosphonate was unable to accelerate union in patients with intertrochanteric fractures. In other words, these drugs led to union with a delay. In this regard, while our findings are in line with the results of some studies, they are not in congruence with some other studies. For instance, Kim TY et al. (2012) evaluated the effect of different times of prescription of bisphosphonates on acceleration of intertrochanteric fracture and concluded that while the prescription of bisphosphonates in one week after fracture led to union on the 10th week, this process had no significant relationship with acceleration of union after the prescription of bisphosphonates on the first and third months. In the end, it was shown that bisphosphonate was unable to accelerate union in patients with intertrochanteric fractures. In this regard, our findings are in line with the aforementioned study since while all patients had a complete union at the end of the 12th week, all subjects in the parathyroid group reported complete union at the end of the eighth week. Nevertheless, there was no significant difference between the groups in terms of the pace of union.

Moreover, Aspenberg and Johansson (2010) marked that teriparatide had an impact on early callus caused by radius distal fracture.
(25), which is not consistent with our results since despite the fact that all patients of the three groups had complete union until the end of the 12th week, all participants in the CinnoPar group had complete union at the end of the eighth week. Nonetheless, there was no significant difference between the groups in terms of the pace of union. In a review by Bodenner et al. (2007) on the effectiveness of teriparatide in osteoporosis treatment, a 20-mg daily dose of parathyroid hormone can accelerate the improvement of fracture and production of new bone with a similar structure of natural bone (26), which is not in accordance with our findings. In a research by Orwoll et al. (2003), the effects of treatment with teriparatide on bone density in male patients with osteoporosis (27). According to the results, treatment with teriparatide increased BMD and was recognized as a potentially beneficial treatment for osteoporosis in men. Our findings demonstrated that CinnoPar and alendronate played no role in the time of repair of distal radius fracture. Attention to these results is importance since our findings are not in congruence with the results of studies performed on the effectiveness of CinnoPar and alendronate in the repair of hip fractures. For instance, Hawley et al. (2016) evaluated anti-osteoporosis treatment and re-fracture in patients with hip fractures in England. The study showed that the interventions to inform physicians about the importance of anti-osteoporosis treatment following hip fractures through the use of guidelines and the availability of alendronate sodium generic increased the rate of administration of anti-osteoporosis drugs by 14.9% made a considerable and important decrease in major fractures and hip re-fractures. In this regard, major and hip fractures decreased by 14% and 22% during the three years, respectively (28). Some of the inconsistencies between the results of the current research with previous studies are due to limitations, such as sample size, which limited the generalization of final results. It is recommended that future studies be performed in other healthcare centers and on other sample sizes and follow-ups be carried out in more time intervals.

### Conclusion

Given the high prevalence of radius distal fracture in old patients diagnosed with osteoporosis and the necessity of quick reunion to return to normal life before the injury and increase life expectancy, our findings demonstrated that none of the osteoporosis treatment methods (bisphosphonate and parathyroid hormone) were able to accelerate the pace of union and only increased treatment costs and medication complications.

### Acknowledgments

Hereby, we extend our gratitude to the participants of the research for assisting us in performing the present study.

### Conflicts of Interest

None declared.

### References


